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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,233	KAYMAKCALAN ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17,21,22,24,31,34,35,42,43,45,48,52-55 and 57-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17,21,22,24,31,34,35,42,43,45,48 and 57-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *52-55* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed August 18, 2009 are acknowledged.

   Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, 52-55 and 57-59 are pending.

   Claims 1-14, 18-20, 23, 25-30, 32-33, 36-41, 44, 46-47, 49-51 and 56 have been canceled.

   Claims 15, 17, 21, 42, 43, 48, 54 and 55 have been amended.

   Claims 57-59 are new.

   Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 57-59 are under examination.

   Claims 52-55 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 12, 2004.

2. This Office Action is in response to applicant's amendment and remarks filed August 18, 2009.

   The previous rejections of record can be found in the Office Action mailed March 18, 2009.

   The previous rejections under 35 U.S.C. § 102(b) and 35 USC 112, 1st paragraph, written description have been withdrawn in view of applicant's amendment to the claims.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

   > (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, and 48 stand rejected and new claim 57 is rejected under 35 U.S.C. § 103(a) as unpatentable over ***Stephens*** et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), in view of ***Salfeld*** et al. (US Patent No. 6,258,562), ***den Broeder*** et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) and ***Kempeni*** (Ann Rheum Dis. 1999 Nov;58 Suppl 1:I70-2), essentially for the reasons of record as put forth in the Office Action mailed March 18, 2009 as described further below.

Applicant argues the claimed invention is not obvious because the cited references allegedly do not teach or suggest the claimed invention and because certain teachings of the cited references allegedly teach away from the claimed invention.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed March 18, 2009.

The Stephens Reference

As stated in the previous Office Action at page 4, 4th paragraph: "Stephens teaches a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571. Stephens further teaches that the disease activity measures included tender and swollen joints, and that patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated (see entire document, in particular pages 326-327). Furthermore, all patients receiving CDP571 scored a reduction in pain scale by week 1 as taught by the following: 'First infusion - *Patients who received placebo did not improve. In contrast, there was a dose-dependent effect of CDP571 treatment* with maximum patient responses after 10 mg/kg...*All patients who received CDP571 scored a reduction in pain scale by week 1*.' See, Stephens, page 327, 1st paragraph, emphasis added."

Applicant's 1st argument about Stephens is as follows (See remarks at page 7, 2nd and 3rd paragraphs, applicant's emphasis shown):

"...the Examiner cites p327, 1st paragraph of Stephens: '[a]ll patients who received CDP571 scored a reduction in pain scale by week 1' (emphasis added). However, the subjective 'pain scale' provided by the patients themselves (see page 326, third paragraph of Stephens) is not relevant to the objective standards recited in the claims. The claimed invention requires that at least one recited symptom - bone erosion, cartilage erosion, inflammation, vascularity, joint distortion, swelling of the joints, joint deformation, or ankylosis on flexion - be alleviated (independent claims 15, 21, 42, and 48). Moreover, the Examiner has provided no evidence of what such a 'pain scale' would have measured.

There is no disclosure in Stephens regarding evidence of symptom relief for the 0.1 mg/kg treatment group commensurate with the required elements of the amended claims..."

Applicant's argument is not found convincing because applicant is arguing against the Stephens reference individually. See MPEP § 707.07(f).

While the claims recite "at least one recited symptom - bone erosion, cartilage erosion, inflammation, vascularity, joint distortion, swelling of the joints, joint deformation, or ankylosis on flexion - be alleviated" as argued by applicant it is ***not*** necessary that the combined reference teachings *explicitly* teach that a patient treated with a low dose of a fully

human anti-TNFα antibody having the physical characteristics recited in the instant claims be alleviated in at least one of bone erosion, cartilage erosion, inflammation, vascularity, joint distortion, swelling of the joints, joint deformation, or ankylosis on flexion in order to render the claimed invention obvious.

Rather, all that is necessary is that the combined reference teachings render obvious the treatment of rheumatoid arthritis with fully human anti-TNFα antibody having the physical characteristics recited in the instant claims and at dosages falling within those recited in the instant claims. If so, then it will necessarily follow that the patient will be alleviated in at least one of the symptoms as recited in the claims.

Applicant's 2nd argument about Stephens is as follows (see remarks pages 7-8, applicant's emphasis is shown):

"…Applicants note that Table 2 on page 328 only shows data for the 1 mg/kg and the 10 mg/kg treatment groups. In fact, a careful examination of the Table 2 data reveals that in the 1 mg/kg treatment group, under the symptom 'Swollen Joints,' the average number of swollen joints failed to decrease, and in fact increased during the treatment period, from 15.0 (pre-infusion) to 16.5 (week 1), 16.0 (week 2), 17.0 (week 4), and 17.0 (week 8). Applicants submit that 'Swollen Joints' is the symptom that most closely correlates 'mean arthritic score,' since the scoring system for mean arthritic score cites swelling deformed joint as a determinant (see page 27, last paragraph of the specification).

With respect to the 'pain scale' data itself, Applicants are unable to verify the extent of the alleged pain reduction in the 0.1 mg/kg treatment group, since such data is not shown in Stephens. However, the 1 mg/kg treatment data clearly shows a worsening trend from week 1 to week 8, despite a seemingly lower pain score on week 1 (4.2). In fact, at week 8, the pain score ballooned to 8.3 from the pre-infusion score of 5.5, a 51% increase. The insignificance of the week 1 pain score, which appears to be the only Stephens data relied upon by the Examiner, is further underscored by the fact that the placebo group also appeared to have a week 1 pain score reduction (from 6.2 to 5.7).

In view of such data, one of skill in the art would conclude that, at 1 mg/kg (which is notably 10-100 times the claimed dose range), the Stephens treatment regimen failed to show that *humanized* anti-TNFα antibody can be used to treat arthritis by alleviating the symptoms recited in independent claims 15, 21, 42, and 48. Moreover, Stephens also fails to show how a *humanized* anti-TNFα antibody can be used to treat arthritis 'as demonstrable by mean arthritic score,' as required by independent claims 15 and 42."

Applicant's argument is not found convincing for a number of reasons.

First, applicant's emphasis on the declining effect of the humanized anti-TNFα CDP571 on RA over time ("the 1 mg/kg treatment data clearly shows a worsening trend from week 1 to

week 8, despite a seemingly lower pain score on week 1 (4.2). In fact, at week 8, the pain score ballooned to 8.3 from the pre-infusion score of 5.5…") is not convincing because one of ordinary skill in the art would not expect a humanized antibody having an ability to induce an anti-idiotypic response and a half life of 5-6 days to have a lasting effect on rheumatoid arthritis symptoms (see Stephens at page 321, 1st paragraph; page 330, 3rd paragraph to page 333, 1st paragraph). Rather, one of ordinary skill in the art would be far more interested in the effect of the CDP571 antibody one week after infusion.

Furthermore, while there was a decrease in the pain score at week 1 for placebo as noted by applicant (from 6.2 to 5.7), the decrease in pain score for the patients receiving 1 mg/kg CDP571 was still greater (from 5.5 to 4.2).

Also in contrast to applicant's argument, *all* patients who received CDP571 scored a reduction in pain scale by week 1 and *both* 1 mg/kg and 10 mg/kg administrations of the humanized anti-TNFα antibody CDP571 demonstrated reduction in patient's global assessment of disease activity of borderline statistical significance versus the placebo (see Stephens at page 327, 4th paragraph). Moreover, as taught by Stephens on page 329, 1st paragraph, "of the changes in the laboratory variables, the fall in CRP was the most marked. At dosages of 1 and 10 mg/kg of CDP571, median CRP concentrations were reduced at week 1 virtually to within the normal range..."

In conclusion, while the data of Stephens is somewhat mixed with respect to the effect of 0.1 mg/kg - 1 mg/kg CDP571 on rheumatoid arthritis, perhaps because of the particular characteristics of the CDP571 antibody - an ability to generate anti-idiotypic responses and thus a shortened half-life as (see applicants' arguments in their remarks at page 10, 2nd paragraph and in the response filed June 4, 2008 at page 8, 2nd paragraph) - in balance, one of ordinary skill in the art would have considered the teachings of Stephens to provide reasonable support for using a low dose of an anti-TNFα antibody to treat rheumatoid arthritis.

Most importantly, when the teachings of Stephens are considered ***in combination*** with the teachings of Den Broeder and Salfeld, one of ordinary skill in the art would have been motivated, and would have had a reasonable expectation of successfully treating a rheumatoid arthritis with a fully human anti-TNFα antibody having the physical characteristics recited in the instant claims and at dosages falling within those recited in the instant claims.

The previous Stephens teaching away argument

Applicant asserts on page 8, 2nd paragraph of their remarks (emphasis added) "…other than relying on the argument that 'Stephens teaches the use of *humanized* anti-TNFα antibody to reduce pain scale by week 1 in *all* patients,' (see above) ***the Examiner has not provided any***

other argument against Applicants' 'teach-away' argument. Applicants submit that the analysis above further strengthens Applicants' previous 'teach away' argument…"

Applicant is invited to reconsider the following section reproduced from the previous Office Action:

"2) Applicant further argues 'One of ordinary skill in the art would not have been motivated, based on the disclosure of Stephens, to treat arthritis with a low dose of 0.01-0.1 mg/kg, since Stephens provides no evidence that a 0.1 mg/kg dose of CDP571 is effective in treating arthritis and, moreover, teaches that a low dose of an antibody mounts an immune response and is cleared from the patient's system to a greater extent than a higher dose, e.g., 10 mg/kg, of CDP571. Applicants therefore urge that Stephens *teaches away* from the claims as amended.'

(see Applicant's remarks filed December 10, 2008, page 7, 2nd paragraph, applicant's emphasis shown).

Considering applicant's second argument first, as stated in the prior Office Action, Stephens teaches a method of treating rheumatoid arthritis comprising administering a single 0.1 mg/kg dose of humanized anti-TNFα antibody, CDP571…

Thus, in contrast to applicant's argument, the examiner's position continues to be that Stephens ***does*** teach the treatment of arthritis with a single dose of 0.1 mg/kg humanized anti-TNFα antibody.

Furthermore, with respect to applicant's argument that Stephens teaches away form the claimed invention, while Stephens does teach increased CPD571 clearance when patients are treated over particular time periods and at particular dosages, i.e., 8 weeks after a single administration of 0.1 mg/kg CDP571 anti-TNFα there is an increase in anti-CDP571 IgG production, and subsequent doses of CDP571 anti-TNFα antibody at 1 or 10 mg/kg resulted in increased CPD571 clearance, this does not negate the other teachings of Stephens that, in contrast to the placebo treatment, treatment with CDP571 anti-TNFα antibody had a dose-dependent effect on the treated patients, and ***all*** patients receiving anti-TNFα antibody scored a reduction in pain scale by week 1.

Thus, while Stephens teaches that under certain limited conditions (which fall within the scope of the instant claims but certainly do not fully encompass the scope of the instantly claimed method) the effectiveness of CDP571 anti-TNFα antibody would expected to be compromised, Stephen's nevertheless teaches that treatment of rheumatoid arthritis with 0.1 mg/kg CDP571 anti-TNFα antibody is effective.

Furthermore, the teachings of Salfeld provide a solution to the issue of CDP571 clearance that would be readily recognized by one of ordinary skill in the art.

In particular, one of ordinary skill in the art would have been motivated to substitute the human D2E7 antibody of Salfeld for the humanized CDP571 antibody of Stephens because, as taught by Salfeld, a fully human antibody, such as D2E7, is preferable to a humanized antibody, such as CDP571, which is 95% human/5% murine, because even a small amount of non-human sequence can elicit an unwanted immune reaction, especially so when administered over long periods of time as in the treatment of chronic rheumatoid arthritis (see Salfeld, paragraph bridging columns 1-2).

With respect to applicant's first argument about the Stephens reference, the examiner disagrees that one of ordinary skill in the art would not 'rely on the teachings of Stephens for any motivation or suggestions regarding dosage or other characteristic of a fully human antibody' because Stephens teaches the use of a humanized rather than a fully human anti-TNFα antibody to treat rheumatoid arthritis.

If anything, the skilled artisan would reasonably expect substitution of a fully human anti-TNFα antibody, such as the D2E7 antibody taught by Salfeld, to be effective at lower doses than the humanized anti-TNFα antibody CDP571 given the reduced immunogenicity of a fully human antibody which results in a longer serum half-life, see e.g., Joachim Kempeni, teaching that D2E7 has a mean serum half-life of around 11.6 to 13.7 days in rheumatoid arthritis patients whereas as shown by Stephens, the half-life of CDP571 is far less

than 10 days at doses encompassed in the instant claims, for example, the CDP571 half-life is 5 days when administered at 0.1 mg/kg. (See Stephens page 321)."

It is the examiner's position that the bold underlined sections reproduced from the previous Office Action are an argument against applicants' previous "teach away" argument.

The Salfeld reference

With respect to the teachings of Salfeld, Applicant argues "…the claimed invention is not only limited by a low dose range (0.01 - 0.1 mg/kg), but also a low frequency of 'not more than once per week.' Although Salfeld does recite the broad range of 0.1 - 20 mg/kg, it does so without concurrently reciting a frequency of administration. In fact, the only time an administration frequency is recited with a dose range is in Example 4, part D, section III (col. 43, lines 6-8), where a thrice a week frequency is used: '[e]ach group received three i.p. injections per week of the indicated treatments' (emphasis added). Therefore, Salfeld fails to disclose the use of any human antibody at both a low dose of 0.1 mg/kg and a frequency of not more than once per week, as recited in all the independent claims.

Furthermore, as argued above, other than the irrelevant and at best questionable 'pain score' in the 0.1 mg/kg treatment regimen, Stephens fails to show any relevant data regarding the 0.1 mg/kg treatment regimen using a *humanized* antibody. Even the 1 mg/kg treatment data is marginal at best. Therefore, even assuming for the sake of argument that one of skill in the art would have been motivated to replace the Stephens antibody with a fully human antibody as taught in Salfeld (which Applicants do not concede), the skilled artisan would at best arrive at an effective dose of about 1 mg/kg, not 0.1 mg/kg (and certainly not *below* 0.1 mg/kg).

Due to the disclosure (or lack thereof) in Salfeld, as discussed above, one of skill in the art would have received no guidance from Salfeld to use a low dose of 0.01 - 0.1 mg/kg of fully human antibody at a frequency of not more than once per week, let alone achieving any of the objective treatment standard as recited in the claims."

See remarks paragraph bridging pages 8-9 to page 9, 2nd paragraph.

Applicant's argument is not found convincing for a number of reasons.

First, it is true that Salfeld recites that an anti-TNFα antibody having the properties recited in the instant claims can be used to treat disease when administered within the range of 0.1 - 20 mg/kg, and that Salfeld recites this dosage range without concurrently reciting a frequency of administration.

However, it is also true that Salfeld teaches this dosage range is a guideline, that dosage regimes are expected by one of ordinary skill in the art to vary with the exigencies of any given therapeutic situation and that the "therapeutically effective amount" of an antibody of

the invention is "an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result." (see cols. 25-26 bridging paragraph).

It is the examiner's position that given the teachings of Stephens and den Broeder as reiterated in the Sections above and below, it would have been obvious to one of ordinary skill in the art that the lower limit of the therapeutic range recited in Salfeld, 0.1 mg/kg fully human anti-TNFα antibody administered once per week would be effective.

The den Broeder reference

Applicant acknowledges den Broeder "discloses that all enrolled patients were either administered D2E7 once every two weeks or once every four weeks. ***Thus, it is entirely possible that all three patients were on the once per two weeks schedule, making the lowest average dose to 0.125 mg/kg per week. Of course, in theory, it may also be possible that at least one of them was indeed on a once per 4 weeks schedule***, making his / her average dose to allegedly fall within the claimed range as suggested by the Examiner."

Applicant continues "As den Broeder fails to provide critical information, the Examiner's argument is based, therefore, on a theoretical *possibility*. Since the obviousness analysis must be based on the *Graham* factual inquiry, Applicants submit that the Examiner's argument is not based on substantial evidence, and thus falls short of the legal requirements mandated under *Graham v. John Deere Co.*" (see Remarks page 10, 1st paragraph, emphasis added).

Applicant's argument is not found convincing because it is ***not*** a "theoretical possibility" that ***at the very least "all three patients were on the once per two weeks schedule, making the lowest average dose to 0.125 mg/kg per week"*** as argued by applicant. Rather, at a minimum den Broeder puts forth this teaching.

Moreover, even if den Broeder ***exclusively*** taught that ***"all three patients were on the once per two weeks schedule, making the lowest average dose to 0.125 mg/kg per week"*** as argued by applicant, as stated in numerous previous Office Actions (see the Office Actions mailed April 18, 2009 at page 8, 1st paragraph; September 10, 2008 at page 4, 2nd paragraph; March 4, 2008 at page 10, last paragraph; August 8, 2007 at page 12, 2nd paragraph; February 8, 2007 at page 11, 2nd paragraph) den Broeder teaches:

"as no smaller dose steps than 0.25 mg/kg were included, one could speculate that even further reduction is possible for individual patients. This is supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNFα, document for…D2E7 (up to 14 weeks EULAR response)..." (see page 641, left column, 2nd paragraph).

These teachings of den Broeder regarding the reasonable possibility of yet further anti-TNFα antibody dose titration are consistent with the teachings of Salfeld that anti-TNFα antibody

dosage is a results effective variable that should be "adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions". Indeed, applicant's assertion at page 8, 1st paragraph of their remarks filed November 8, 2007 that "[e]ven if, *arguendo,* some testing would be required to determine if the dose is affective on a particular patient, such experimentation would certainly not be 'undue' for a skilled artisan, since drug dosages have to be optimized for each patient regardless," is further consistent with this idea.

Thus, one of ordinary skill in the art would have been motivated, and would have a reasonable of expectation of success, in treating at least some rheumatoid arthritis patients with the fully human anti-TNFα antibody described by Salfeld at a dose of at least as low as 0.1 mg/kg per week, just 0.025 mg/kg below the lowest average dose of 0.125 mg/kg per week of den Broeder.

Claims reciting "…administering…a low dose of *about 0.1 mg/kg…*"

In addition to the reasoning put forth above, amended claims 15, 48 and 57, and dependent claims thereof are further obvious because they recite that the method comprises "…administering…a low dose of *about 0.1 mg/kg…*"

The specification does not provide any explicit guidance as to what sort of doses are encompassed by the phrase "a low dose of *about 0.1 mg/kg"*.

Thus, this phrase, given its broadest reasonable interpretation consistent with the instant specification and with the plain meaning of the term "about" to one of ordinary skill in the art, encompasses in its breadth treatment with the claimed antibody at doses both lesser than, and greater than, 0.1 mg/kg.

As acknowledged by applicant, den Broeder "discloses that all enrolled patients were either administered D2E7 once every two weeks or once every four weeks. Thus, ***it is entirely possible that all three patients were on the once per two weeks schedule, making the lowest average dose to 0.125 mg/kg per week***. Of course, in theory, it may also be possible that at least one of them was indeed on a once per 4 weeks schedule, making his / her average dose to allegedly fall within the claimed range as suggested by the Examiner." (see remarks at page 10, 1st paragraph, emphasis added).

Since, in the absence of evidence to the contrary, 0.125 mg/kg/week or even 0.25 mg/kg/biweek would be considered by one of ordinary skill in the art to be "about 0.1 mg/kg," it is not necessary for the cited references to teach anything more than treating rheumatoid arthritis using a fully human anti-TNFα antibody taught by Salfeld at the aforementioned dosages which are greater than, but "about 0.1 mg/kg", such as 0.125 mg/kg/week or 0.25 mg/kg/biweek to render the invention of claims 15, 48 and 57, and dependent claims thereof obvious.

Conclusion

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 21, 22, 24, 31, 34, 35, 42, 43, and 45 stand rejected, and new claim 57 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating arthritis with about 0.1 mg/kg of a fully human anti-TNFα antibody having the physical properties recited in claim 1, ***does not reasonably provide enablement for*** treating arthritis with 0.01-0.1 mg/kg of a fully human anti-TNFα antibody having the physical properties recited in claim 1, or for methods of treatment employing the "D2E7" anti-TNFα antibody.

The D2E7 anti-TNFα antibody

With respect to claims 34, 35 and 45 reciting "wherein the anti-TNFα antibody is...D2E7" applicant argues the D2E7 anti-TNFα antibody is commercially available as HUMIRA (adalimumab) and therefore it is available to the public.

Applicant's argument has been considered but has not been found convincing.

First, the website applicant points to in support of the commercial availability of HUMIRA (adalimumab) makes no mention of "D2E7". Thus, applicant has not provided objective evidence that the D2E7 anti-TNFα antibody taught, e.g., by Salfeld, is the same thing as the *currently* commercially available HUMIRA (adalimumab) antibody.

Second, the website applicant points to in support of the commercial availability of HUMIRA (adalimumab) does not disclose when the antibody was first commercially available. Thus, even if applicant were able to establish with objective evidence that the D2E7 antibody = the commercially available HUMIRA (adalimumab), applicant would further need to establish with objective evidence that the commercially available HUMIRA (adalimumab) antibody was available to the public as of applicant's date of invention, see MPEP § 2164.05(a).

Treatment with 0.01 - 0.1 mg/kg

With respect to treating arthritis with 0.01 - 0.1 mg/kg of a fully human TNFα antibody, applicant argues their amendments to claims 21 and 42, and dependent claims thereof, render the outstanding rejection of record moot (see remarks at page 14, 4th paragraph to page 15, 1st paragraph). While it is not exactly clear why applicant believes the amended claims render the previous rejection of record moot, one possibility is that applicant believes 1. the claimed method to be limited to administering the anti-TNFα for at least 10 treatments at a frequency of not more than once per week and 2. that such a limitation addresses the outstanding rejections of record.

Applicant's argument has been considered but has not been found convincing.

First, applicant's amendment does not limit the claimed method to administering the anti-TNFα for at least 10 treatments at a frequency of not more than once per week.

The instant claims recite "A low dose method for alleviating at least one symptoms associated with arthritis comprising administering…a low dose of 0.01 - 0.1 mg/kg at a frequency of not more than once per week, such that alleviation of at least one symptom selected from the group consisting of bone erosion, cartilage erosion…is demonstrable after 10 treatments, wherein the anti-TNFα antibody, or antigen-binding portion thereof, dissociates from human TNFα with a Kd of…."

This claim, given its broadest reasonable interpretation consistent with the instant specification, reads on treating a patient with 0.01 - 0.1 mg/kg at a frequency of not more than once per week, wherein the patient may be treated for fewer than 10 treatments, e.g., for 9 treatments ***AND*** wherein the patient may be treated for 10 or more treatments. While the claim recites "such that alleviation of at least one symptom selected from the group consisting of bone erosion, cartilage erosion…is demonstrable after 10 treatments" this does ***not*** limit the claim to administering 10 or more treatments to the subject to be treated. If the claim recited something like "A low dose method for alleviating at least one symptoms associated with arthritis comprising administering…***at least 10 treatments of*** a low dose of 0.01 - 0.1 mg/kg at a frequency of not more than once per week, such that alleviation of at least one symptom selected from the group consisting of bone erosion, cartilage erosion…is demonstrable after 10 treatments…" then the claim would be limited to administering 10 or more treatments to the subject to be treated.

Secondly, even if applicant were to limit the claimed method to administering the anti-TNFα for at least 10 treatments at a frequency of not more than once per week this still would not address the outstanding rejections of record for the reasons put forth in the previous Office Actions (see Office Action mailed March 18, 2009 at page 14, 2nd paragraph to page 15 as

well as the Office Action mailed March 4, 2008 at page 3, 6th paragraph to page 5, last paragraph).

In conclusion, undue experimentation would be required to produce the invention commensurate with the breadth of the claims based on the disclosure of the instant specification and the knowledge in the art. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 stand rejected, and new claim 57 is rejected, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1–7, 17, 19, 20, 36-39, 49, 51, 52, 68, 69 and 70 of U.S. Patent No. 6,509,015 in view of Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), Salfeld et al. (US Patent No. 6,258,562), den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) and Joachim Kempeni (Ann Rheum Dis. 1999 Nov;58 Suppl 1:I70-2), essentially for the reasons of record as put forth in the Office Action mailed March 18, 2009.

Applicant argues the amended claims are not obvious over the reference claims and secondary teachings because they allegedly do not teach the claimed invention.

Applicant's argument has been considered, but has not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed March 18, 2009 and for the reasons put forth in Section 6 above.

Thus, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

9. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 stand rejected, and new claim 57 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 7,223,394 in view of Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), Salfeld et al. (US Patent No. 6,258,562), den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) and Joachim Kempeni (Ann Rheum Dis. 1999 Nov;58 Suppl 1:I70-2), essentially for the reasons of record as put forth in the Office Action mailed March 18, 2009.

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Thus, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

10. Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 stand rejected, and new claim 57 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17, 41, 79, 86, 103, 110, 115, 122, 127 and 134 of USSN 11/233,252 (U.S. 20060024293), in view of Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, Fla.), Salfeld et al. (US Patent No. 6,258,562), den Broeder et al. (Rheumatology (Oxford). 2002 Jun;41(6):638-42) and Joachim Kempeni (Ann Rheum Dis. 1999 Nov;58 Suppl 1:I70-2), essentially for the reasons of record as put forth in the Office Action mailed March 18, 2009.

Applicant argues the amended claims are not obvious over the reference claims and secondary teachings because they allegedly do not teach the claimed invention.

Applicant's argument has been considered, but has not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed March 18, 2009 and for the reasons put forth in Section 6 above.

Thus, the reference claims, in view of the teachings of Stephens, Salfeld, den Broeder and Joachim Kempeni, render the claimed invention obvious.

A new grounds of rejection follows.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. New claims 58 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Le et al. (U.S. 6,277,969, cited previously).

Le teaches a method for treating arthritis comprising administering to a subject the anti-TNFα antibody infliximab at a dose of 0.5 mg/kg, for example, once per week (see column 36, 1st and 2nd paragraphs). Le also exemplifies the treatment of human arthritis patients with about 0.5 mg/kg (1.0 mg/kg was used) showing a decrease in arthritis symptoms in these patients, such as decreased swollen joint counts, i.e., decreased inflammation (see columns 80-89, including Table 16).

Thus, Le anticipates the instant claims.

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644